

*Pursuant to 37 C.F.R. §1.121, the following is a complete listing of the claims of the present application:*

1. (Original) A non-murine antibody that competes with monoclonal antibody RX1 for binding to M-CSF by more than 75%, wherein said monoclonal antibody RX1 comprising the heavy chain and light chain amino acid sequences set forth in SEQ ID NOs: 2 and 4, respectively.
2. (Original) The antibody of claim 1 that specifically binds to the same epitope of M-CSF as monoclonal antibody RX1, wherein said monoclonal antibody RX1 comprises the heavy chain and light chain amino acid sequences set forth in SEQ ID NOs: 2 and 4, respectively.
3. (Original) The antibody of claim 2 that binds an epitope of M-CSF that comprises at least 4 contiguous residues of SEQ ID NO: 120 or 121.
4. (Original) The antibody of claim 2 that binds an epitope of M-CSF that comprises SEQ ID NO: 120 or 121.
5. (Cancelled)
6. (Previously Presented) The antibody of any of claims 1-4 that is a chimeric antibody, a humanized antibody, a human engineered antibody, a human antibody, a single chain antibody, a monoclonal antibody, an IgG antibody, Fab fragment, an F (ab')<sub>2</sub> fragment, an Fv fragment, or a single chain Fv fragment.
- 7 – 8. (Cancelled)
9. (Previously Presented) The antibody of claim 1 that retains an affinity K<sub>d</sub> (dissociation equilibrium constant) with respect to M-CSF of SEQ ID NO: 9 of at least 10<sup>-7</sup> M or higher.
- 10 -11. (Cancelled)

12. (Previously Presented) The antibody of claim 1 that comprises an amino acid sequence 90% identical to SEQ ID NO: 24.

13. (Cancelled)

14. (Previously Presented) The antibody of claim 1 that comprises at least 1 of SEQ ID NOs: 18, 21, 24, 29, 32, and 36.

15. – 19. (Cancelled)

20. (Previously Presented) The antibody of claim 14 that further comprises one or more of SEQ ID NOs: 16, 17, 18, 19, 20, 21, 22, 23, 25, 26, 27, 28, 29, 30, 32, 33, 34, 35, 37, and 38.

21. – 23. (Cancelled)

24. (Previously Presented) The antibody of claim 14 in which at least one amino acid within a CDR is substituted by a corresponding residue of a corresponding CDR of another anti-MCSF antibody.

25. (Previously Presented) The antibody of claim 14 comprising a variable light chain amino acid sequence which is at least 65% homologous to the amino acid sequence set forth in SEQ ID NO : 4.

26. (Previously Presented) The antibody of claim 14 comprising a variable heavy chain amino acid sequence which is at least 65% homologous to the amino acid sequence set forth in SEQ ID NO: 2.

27. (Previously Presented) The antibody of claim 6 comprising a constant region of a human antibody sequence and one or more heavy and light chain variable framework regions of a human antibody sequence.

28. (Original) The antibody of claim 27 wherein the human antibody sequence is an individual human sequence, a human consensus sequence, an individual human germline sequence, or a human consensus germline sequence.

29. (Original) The antibody of claim 27 that comprises a fragment of an IgG1 constant region.

30. (Original) The antibody of claim 29 that comprises a mutation in the IgG1 constant region that reduces antibody-dependent cellular cytotoxicity or complement dependent cytotoxicity activity.

31. (Original) The antibody of claim 27 that comprises a fragment of an IgG4 constant region.

32. (Original) The antibody of claim 31 that comprises a mutation in the IgG4 constant region that reduces formation of half-antibodies.

33. (Currently Amended) The antibody of claim 6, comprising a heavy chain variable region that comprises the amino acid sequence selected from the group consisting of:

(a)XVXLXEXGXXXXXXXXXXLXLXCXVDYSITSDYAWNWIQXXXX  
XLXWMGYISY[;]  
SGSTSNXXLXXXIXIXRXXXXXXFXLXLXXVXXXDXAXYYCASFDYAHAMDYW  
GXGTXVXVXX (SEQ ID NO: 124),

(b)DVXLXEXGPXXVXPXXXLXLXCXVTDYSITSDYAWNWIQXPXX  
KLEWMGYISYS  
GSTSYNPSLKXRIXIXRXTXXNXFXLXLXXVXXXDXATYYCASFDYAHAMDYWG  
GTXVXVXX (SEQ ID NO: 125);

(c)XVQLQESGGLVKPSQXLSLTCTVXDYSITSDYAWNWIQFPGXXL  
EWMGYISYSGS  
TSYNPSLKSRIXIXRDTSKNQFXLQLNSVTXXDTAXYYCASFDYAHAMDYWGQGT  
XVTVSS (SEQ ID NO: 126);

(d)DVQLQESGGLVKPSQXLSLTCTVTDYSITSDYAWNWIQFPGXKL  
EWMGYISYSGS  
TSYNPSLKSRIXIXRDTSKNQFXLQLNSVTXXDTATYYCASFDYAHAMDYWGQGT  
XVTVSS (SEQ ID NO: 127);

(e)DVQLQESGPGLVKPSQTLSTCTVTDYSITSDYAWNWIWIRQFPGKKL  
EWMGYISYSGS  
TSYNPSLKSRTISRDTSKNQFSLQLNSVTAADTATYYCASFDYAHAMDYWGQGTTV  
TV SS (SEQ ID NO: 41); and

(f)QVQLQESGPGLVKPSQTLSTCTVSDYSITSDYAWNWIWIRQFPGKGLE  
WMGYISYSGS  
TSYNPSLKSRTISRDTSKNQFSLQLNSVTAADTAVYYCASFDYAHAMDYWGQGT  
VTV SS (SEQ ID NO: 43);

wherein X is any amino acid.

34-38. (Cancelled)

39. (Currently Amended) The antibody of claim 6, comprising a light chain variable region that comprises the amino acid sequence selected from the group consisting of:

(a)XIXLXQXXXXXXXXVXXXXXVFXCXAXQSIGTSIHWYXQXXXXXP  
XLLIKYASEXX  
XXIXXXFXGXGXGXXFXLXIXXVXXXDXADYYCQQINSWPTTFGXGTXLXXXXX  
(SEQ ID NO: 128);

(b)XIXLXQXPXXLXVXPXXXVFXCXASQSIGTSIHWYQQXTXXSPRL  
LIKYASEXISXI  
PXRFXGXGXGXXFXLXIXXVXXXDXADYYCQQINSWPTTFGXGTXLXXXXX (SEQ ID NO: 129);

(c)XIXLTQSPXXLSVSPGERVXFSCRASQSIGTSIHWYQQXTXXXPRLLI  
KYASEXXXGIP  
XRFSGSGSGTDFTLXIXXVESEXDXADYYCQQINSWPTTFGXGTXKLEIKRX (SEQ ID NO: 130);

(d)XIXLTQSPXXLSVSPGERVXFSCRASQSIGTSIHWYQQXTXXXPRLLI  
KYASEXISGIPX

RFSGSGSGTDFTLXIXXVESEDXADYYCQQINSWPTTFGXGTKLEIKRX (SEQ ID NO: 131);

(e)XIXLTQSPXXLSVSPGERVXFSCRASQSIGTSIHWYQQXTXXXPRLLI  
KYASESISGIPX  
RFSGSGSGTDFTLXIXXVESEDXADYYCQQINSWPTTFGXGTKLEIKRX (SEQ ID NO: 132);

(f)EIVLTQSPGTLVSPGERVTFSCRASQSIGTSIHWYQQKTGQAPRLLI  
KYASESISGIPD  
RFSGSGSGTDFTLTISRVESEDFADYYCQQINSWPTTFGQGTKLEIKRT (SEQ ID NO: 45);

(g)EIVLTQSPGTLVSPGERVTFSCRASQSIGTSIHWYQQKTGQAPRLLI  
KYASERATGIP  
DRFSGSGSGTDFTLTISRVESEDFADYYCQQINSWPTTFGQGTKLEIKRT (SEQ ID NO: 47); and

(h)EIVLTQSPGTLVSPGERVTFSCRASQSIGTSIHWYQQKTGQSPRLLI  
KYASERISGIPD  
RFSGSGSGTDFTLTISRVESEDFADYYCQQINSWPTTFGQGTKLEIKRT (SEQ ID NO: 48);

wherein X is any amino acid.

40-46. (Cancelled)

47. (Previously Presented) The antibody of any of claims 33 or 39 wherein at least one X is the same as an amino acid at the same corresponding position in SEQ ID NOs: 2 or 4 using Kabat numbering.

48. (Previously Presented) The antibody of any of claims 33 or 39, wherein at least one X is a conservative substitution of an amino acid at the same corresponding position in SEQ ID NOs: 2 or 4 using Kabat numbering.

49. (Cancelled)

50. (Previously Presented) The antibody of any of claims 33 or 39, wherein at least one X is an amino acid at the same corresponding position within a human antibody sequence, using Kabat numbering.

51. (Previously Presented) The antibody of any of claims 33 or 39, wherein at least one X is an amino acid at the same corresponding position within a human consensus antibody sequence, using Kabat numbering.

52. (Original) The antibody of claim 50 wherein the human antibody sequence is a human consensus sequence, human germline sequence, human consensus germline sequence, or any one of the human antibody sequences in Kabat.

53. (Previously Presented) The antibody of claim 6 comprising any one of the heavy chain sequences set forth in SEQ ID NOS: 41, 43, 114, 116, or 119.

54. (Cancelled)

55. (Previously Presented) The antibody of claim 6 comprising any one of the light chain sequences set forth in SEQ ID NOS: 45, 47, 48, 51, 53 or 136.

56. (Original) The antibody of claim 1 comprising the heavy chain sequence set forth in SEQ ID NO: 114 and the light chain sequence set forth in SEQ ID NO: 47.

57. (Original) The antibody of claim 1 comprising the heavy chain sequence set forth in SEQ ID NO: 116 and the light chain sequence set forth in SEQ ID NO: 47.

58. (Original) The antibody of claim 1 comprising the heavy chain sequence set forth in SEQ ID NO: 119 and the light chain sequence set forth in SEQ ID NO: 47.

59. (Previously Presented) The antibody of any of claims 33 or 39 comprising a variable heavy chain amino acid sequence which is at least 65% identical to the variable heavy chain amino acid sequence set forth in SEQ ID NOS: 41 or 43.

60. (Original) The antibody of claim 59 comprising a variable heavy chain amino acid sequence which is at least 80% identical to the variable heavy chain amino acid sequence set forth in SEQ ID NOs: 41 or 43.

61. (Previously Presented) The antibody of any of claims 33 or 39 comprising a variable light chain amino acid sequence which is at least 65% identical to the variable light chain amino acid sequence set forth in SEQ ID NOs: 45,47, 48, 51, or 53.

62. (Original) The antibody of claim 61 comprising a variable light chain amino acid sequence which is at least 80% identical to the variable light chain amino acid sequence set forth in SEQ ID NOs: 45,47, 48, 51, or 53.

63. (Previously Presented) An antibody comprising a heavy chain as set forth in claim 59 and a light chain as set forth in of claim 61.

64. (Previously Presented) The antibody of any of claims 12, 14, 20, 24-46, 53, 55-58 and 63 that has an affinity  $K_d$  of at least  $10^{-7}$ .

65. (Original) The antibody of claim 64 that has an affinity  $K_d$  of at least  $10^{-9}$ .

66. – 78. (Cancelled)

79. (Previously Presented) A pharmaceutical composition comprising any one of the antibodies of claims 1-65 or 76 an antibody of claim 1, and a pharmaceutically suitable carrier, excipient or diluent.

80. (Original) The pharmaceutical composition of claim 79 further comprising a second therapeutic agent.

81. (Original) The pharmaceutical composition of claim 80 wherein the second therapeutic agent is a cancer chemotherapeutic agent.

82. (Original) The pharmaceutical composition of claim 80 wherein the second therapeutic agent is a bisphosphonate.

83. (Original) The pharmaceutical composition of claim 82 wherein the bisphosphate is zoledronate, pamidronate, clodronate, etidronate, tiludronate, alendronate, or ibandronate.

84. (Original) The pharmaceutical composition of claim 80 wherein the second therapeutic agent is another antibody.

85. (Previously Presented) The antibody of claim 1 that binds to M-CSF for preventing a subject afflicted with a disease that causes or contributes to osteolysis, wherein said antibody effectively reduces the severity of bone loss associated with the disease.

86. (Previously Presented) The antibody of claim 1 that binds to M-CSF for treating a subject afflicted with a disease that causes or contributes to osteolysis, wherein said antibody effectively reduces the severity of bone loss associated with the disease.

87. (Original) The antibody according to claim 86 wherein said disease is selected from the group consisting of metabolic bone diseases associated with relatively increased osteoclast activity, including endocrinopathies (including hypercortisolism, hypogonadism, primary or secondary hyperparathyroidism, hyperthyroidism), hypercalcemia, deficiency states (including rickets/osteomalacia, scurvy, malnutrition), chronic diseases (including malabsorption syndromes, chronic renal failure (including renal osteodystrophy), chronic liver disease (including hepatic osteodystrophy) ), drugs (including glucocorticoids (glucocorticoid-induced osteoporosis), heparin, alcohol), and hereditary diseases (including osteogenesis imperfecta, homocystinuria), cancer, osteoporosis, osteopetrosis, inflammation of bone associated with arthritis and rheumatoid arthritis, periodontal disease, fibrous dysplasia, and/or Paget's disease.

88. (Previously Presented) The antibody according to claim 1 that binds to M-CSF for preventing or treating metastatic cancer to bone, wherein the metastatic cancer is breast, lung, renal, multiple myeloma, thyroid, prostate, adenocarcinoma, blood cell malignancies, including leukemia or lymphoma; head or neck cancers; gastrointestinal cancers, including esophageal cancer, stomach cancer, colon cancer, intestinal cancer, colorectal cancer, rectal cancer, pancreatic cancer, liver cancer, cancer of the bile duct or gall bladder; malignancies of the female genital tract, including ovarian carcinoma, uterine



endometrial cancers, vaginal cancer, or cervical cancer; bladder cancer; brain cancer, including neuroblastoma ; sarcoma, osteosarcoma; or skin cancer, including malignant melanoma or squamous cell cancer.

89. – 135. (Cancelled)

136. (Previously Presented) A kit comprising a therapeutically effective amount of the antibody of claim 1, packaged in a container, such as a vial or bottle, and further comprising a label attached to or packaged with the container, the label describing the contents of the container and providing indications and/or instructions regarding use of the contents of the container to prevent or reduce bone loss.

137. (Previously Presented) A kit comprising a therapeutically effective amount of the antibody of claim 1, packaged in a container, such as a vial or bottle, and further comprising a label attached to or packaged with the container, the label describing the contents of the container and providing indications and/or instructions regarding use of the contents of the container to a patient afflicted with a disease that causes or contributes to osteolysis.

138. (Original) The kit of claim 137 wherein said disease is selected from the group consisting of metabolic bone diseases associated with relatively increased osteoclast activity, including endocrinopathies (including hypercortisolism, hypogonadism, primary or secondary hyperparathyroidism, hyperthyroidism), hypercalcemia, deficiency states (including rickets/osteomalacia, scurvy, malnutrition), chronic diseases (including malabsorption syndromes, chronic renal failure (including renal osteodystrophy), chronic liver disease (including hepatic osteodystrophy) ), drugs (including glucocorticoids (glucocorticoid-induced osteoporosis), heparin, alcohol), and hereditary diseases (including osteogenesis imperfecta, homocystinuria), cancer, osteoporosis, osteopetrosis, inflammation of bone associated with arthritis and rheumatoid arthritis, periodontal disease, fibrous dysplasia, and/or Paget's disease.

139. (Previously Presented) A kit comprising a therapeutically effective amount of the antibody of claim 1, packaged in a container, such as a vial or bottle, and further comprising a label attached to or packaged with the container, the label describing the contents of the container and providing indications and/or instructions regarding use of the contents of the container to prevent or treat metastatic cancer to bone.

140. (Original) The kit of claim 139 wherein the metastatic cancer is breast, lung, renal, multiple myeloma, thyroid, prostate, adenocarcinoma, blood cell malignancies, including leukemia or lymphoma ; head or neck cancers; gastrointestinal cancers, including esophageal cancer, stomach cancer, colon cancer, intestinal cancer, colorectal cancer, rectal cancer, pancreatic cancer, liver cancer, cancer of the bile duct or gall bladder; malignancies of the female genital tract, including ovarian carcinoma, uterine endometrial cancers, vaginal cancer, or cervical cancer; bladder cancer; brain cancer, including neuroblastoma; sarcoma, osteosarcoma; or skin cancer, including malignant melanoma or squamous cell cancer.

141. (Previously Presented) A kit comprising a therapeutically effective amount of the antibody of claim 1, packaged in a container, such as a vial or bottle, and further comprising a label attached to or packaged with the container, the label describing the contents of the container and providing indications and/or instructions regarding use of the contents of the container to treat cancer.

142. (Original) The kit of any of claims 136-141 further comprising a second therapeutic agent.

143. (Original) The kit of claim 142 wherein the second therapeutic agent is a cancer chemotherapeutic agent.

144. (Original) The kit of claim 142 wherein the second therapeutic agent is a non-M-CSF colony stimulating factor, or anti-RANKL antibody, or soluble RANKL receptor.

145. (Original) The kit of claims 142 wherein the second therapeutic agent is a bisphosphonate.

146. (Original) The kit of claim 145 wherein the bisphosphonate is zoledronate, pamidronate, clodronate, etidronate, tiludronate, alendronate, or ibandronate.

147. (Previously Presented) The kit of claim 146 including instructions to treat a patient precluded from receiving bisphosphonate treatment.

148. (Previously Presented) The kit of claim 147 comprising a dose of antibody effective to reduce the dosage of second therapeutic agent required to achieve a therapeutic effect.

149. (Previously Presented) The kit of claim 147 comprising a synergistic dose of antibody.

150. (Previously Presented) The kit of claim 147 comprising a dose of antibody effective to inhibit osteoclast proliferation and/or differentiation induced by tumor cells.

151. (Previously Presented) The kit of claim 147 comprising a dose of antibody between about 2 pg/kg to 30 mg/kg body weight.

152. (Original) The kit of claim 151 comprising a dose of antibody between about 0.1 mg/kg to 30 mg/kg body weight.

153. (Original) The kit of claim 152 comprising a dose of antibody between about 0.1 mg/kg to 10 mg/kg body weight.

154. – 161. (Cancelled)